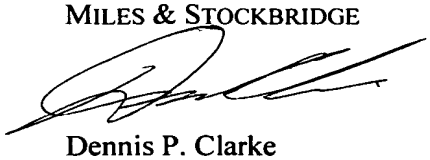
REMARKS

Applicants have earnestly endeavored to place this application in condition for allowance and an early action to that end is respectfully requested.

Respectfully submitted,

MILES & STOCKBRIDGE



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IN THE SPECIFICATION – VERSION WITH MARKINGS TO SHOW CHANGES MADE

Page 4, line 20, "patent" should read --potent--, as indicated below.

(Amended) Disadvantages of anti-diarrheal medicaments, i.e., those referred to in professional papers rather than those medicaments of this type applied in practice, include their secondary strong effects such as antihypertensive effects (clonidine), growth factors (somatostatin), habituation and/or incomplete preclinical research (encephalin derivatives). The application of large doses of antibiotics and long administration thereof has not proved optimum in epidemical diarrhea localities. Where the diarrhea-inducing agent is cholera toxin, however, there does not exist any efficient protection, exception for inoculum which is not sufficiently potent [patent] either, and gives short-term protection only (3 months) and low efficiency (30-40%).

Page 6, line 14, "polyamiries" should read –polyamines--, as indicated below.

Page 6, line 16, "poly(etbylenimine) should read --poly(ethylenimine)--, as indicated below.

Page 7, line 1, "Polyetbyleneimine" should read –polyethylenimine--, as indicated below.

Page 7, line 2, "9O4" should read with numeric zero –904--, as indicated below.

Page 7, line 2, "end" should read –and--, as indicated below.

Page 7, line 2, "Spermadine" should read –Spermidine--, as indicated below.

(Amended) In a series of studies, Tansy was able to demonstrate that polyamiries [polyamines] have a profound impact on the mitility of the gastrointestinal (UI) tract. The original work focused on [poly(etbylenimine)] poly(ethylenimine) and gastric emptying in rodents and dogs. Branched-chain poly(ethylenimine)s effected significant inhibition

of gastric emptying in rodents; however, they caused a severe retch response in dogs. Because of the structural relationship between the poly(ethylenimine)s and natural polyamines, Tansy elected to evaluate the effect of spermidine, spermine, and a group of polyamine analogues on the gastric emptying of rodents. It soon became clear that polyamines had a substantial influence on gastric emptying and that "endogenous spermine and spermidine may have some unrecognized GI secretomotor activity". [See Spermine and Spermidine as Inhibitors of Gastrointestinal Motor Activity, Surg. Gyn. Obst, **1982**, 154, 74-80; Pharmacology of [Polyetbyleneimine] Polyethylenimine I: Effects on Gastric Emptying In Rats, J. Pharm. Sci. **1977**, 66. 899-901; GI Pharmacology of Polyethylenimine II: Motor Activity in Anesthesthetized Dogs, J. Pharm Sci. **1977**, 66,902-[9O4] 904; Effects of Spermine [end Spermadine] and Spermidine on Gastric Emptying in Rats, J. Pharm. Sci **1981**, 70 347]. From a structure-activity perspective, it also became obvious that minor changes in the polyarnine's structure could completely eradicate the molecule's ability to inhibit gastric emptying. These studies strongly suggested that the polyarnine pharmacophore was an excellent candidate for the construction of antitransit, antidiarrheal drugs.

IN THE CLAIMS – VERSION WITH MARKINGS TO SHOW CHANGES MADE IN THE CLAIMS

Claims 9-14, line 1 of each, please replace "A" with --The--.

9. [A] The method according to claim 8 wherein Q is connected either *cis* or trans as the (1,2), (1,3), (1,4), (1,5) or (1,6) isomer.

10. [A] The method according to claim 8 wherein Q is cyclohexyl.

11. [A] The method according to claim 8 wherein x is 3 and y is 3.

12. [A] The method according to claim 8 wherein x is 3, y is 3, R_1 and R_3 are both H and R_2 and R_4 are both ethyl.

13. [A] The method according to claim 8 wherein Q is cyclohexyl; x and y are 3; R_1 and R_3 are both H, and R_2 and R_4 are both ethyl.

14. [A] The method according to claim 13 wherein said polyamine is the *trans* (1,4) isomer.